Correlation of Diffusion Tensor Imaging (DTI) measures with memory dysfunction scores in hypothyroid patients

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Target audience: Researchers working in the field of endocrine disorders**.**

Purpose: In recent years, hypothyroidism has become a common problem among population worldwide. Neuropsychologically, several studies have shown cognitive deficits in attention, language, memory, depressive mood, motor speed and visuospatial skills in hypothyroidism[1]. Few neuroimaging studies have shown cognitive deficits in hypothyroidism using functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS). Diffusion Tensor Imaging (DTI) is a promising MRI technique that measures the strength and direction of water diffusivity in brain parenchyma to estimate the microstructural changes of the brain. Several studies have shown brain abnormalities in relation to neurocognitive dysfunction in diseased conditions. The aim of the present study was to correlate DTI measures and memory dysfunction scores (MDS) in hypothyroid patients.

Materials and Methods: In this study, we have taken eight control subjects (mean age ± SD = 30.9±8.28) and eight hypothyroid patients (mean age ± SD = 32.8±9.22). The informed consent was obtained from all the subjects prior to MRI study. All the patients recruited for the study were diagnosed with hypothyroidism for the first time and had not been treated earlier. Thyroid function tests, namely, free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were carried out in all hypothyroid patients and control subjects. The thyroid function tests were in the normal range for controls (FT3 = 2.8-7.1 pmol/l, FT4 =12.0-22.0 pmol/l and TSH = 0.27-4.2 µIU/ml). In hypothyroid group, patients with FT4 below normal and TSH of atleast 20 µIU/ml or above were recruited for the study. None of the subject had any history of neurological or psychiatric disorders. The study was approved by the Institutional ethics committee. PGI-memory scale (PGIMS) test battery[2] was performed prior to MRI in both the hypothyroid patients as well as healthy controls.

Imaging was performed on a 3-Tesla MRI scanner (Megnetom, Skyra, Siemens) with a 24 channel head and neck coil and 25 mT/m actively shielded gradient system. The conventional MR imaging was done prior to DTI to rule out any structural abnormality using routine T2-weighted turbo spin-echo sequence. DTI data were acquired using a single-shot echo-planar dual SE sequence in 30 directions with ramp sampling. Diffusion-weighted acquisition parameters were: b-factor= 0 and 1000 s/mm^2, slice thickness=3 mm with no interslice space, number of slices=45, FOV=230 mm×230 mm, matrix size = 128 × 128, spatial resolution = 1.797 mm X 1.797 mm X 3mm, flip angle 90°, TR = 8800 ms, TE = 95 ms and NEX=2. Fibre assignment by continuous tracking (FACT) algorithm was used for reconstruction of fibres. An in-house-developed JAVA-based software was used to generate and quantify major white matter (WM) fibre tracts. Details of the generation of the white matter fibre tracts are described in detail elsewhere[3].

Statistical analysis: Independent sample 't' test was performed to see the difference in MDS and fractional anisotropy (FA) and mean diffusivity (MD) values between controls and hypothyroid patient group. Pearson's correlation coefficient was performed to study the relationship between the WM tract specific DTI measures and MDS. A p value ≤0.05 was considered to be statistically significant. All statistical analysis was conducted using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL).

Results: Student's independent t test revealed that the hypothyroid group had significantly higher MDS (8.75 ± 3.96) than the control group (3.50 ± 2.00, p=0.005). On conventional MR imaging, no abnormalities were found in patient group. Out of all the major WM fibres quantitated in our study, significantly decreased FA values were observed in uncinate fasciculus (RUNC & LUNC), cortico spinal tracts (RCST & LCST), fornix (FX) and inferior longitudinal fasciculus (LILF) in hypothyroid patients compared with healthy controls. Cingulum (LCNG), inferior fronto-occipital fasciculus (RIFO & LIFO) and anterior thalamic radiation (RATR) fibres showed decreasing trend in FA values in hypothyroid patients compared with controls, but it did not reach at the level of statistical significance. However, significant increased MD values were observed in arcuate fasciculus (RAF), RUNC, LUNC, superior thalamic radiation (RSTR), LCNG, RIFO, RATR, RILF and LILF regions in hypothyroid group as compared to controls.

Among all WM tracts, in hypothyroid patients significant inverse correlation of MDS with mean FA values was observed in RIFO and LIFO (Table I and Figure 1). Only RATR showed significant positive correlation between MD values and MDS in hypothyroid patients (Table I and Figure 1). In healthy controls, no relationship was observed between DTI measures and memory scores.

Discussion: To the best of our knowledge, this is the first study to report correlation between DTI measures of WM fibre tracts and MDS in hypothyroidism. Our findings showed significant inverse correlation of MDS with FA values in IFO in hypothyroid patients. It is reported that IFO fibres are mainly involved in reading, attention, memory and visuospatial processing task[4]. Therefore, alterations in the connections within circuits might be responsible for the observed memory impairment in hypothyroid patients. There are few studies which have shown that working memory is impaired in hypothyroid patients[5]. Walsh et al. have also suggested that lesions to IFO affect object working memory performance, presumably by disrupting communication between brain areas preferentially involved in the task[6]. Alongwith it, RATR showed positive correlation between MD value and MDS in hypothyroid patients. The increased MD in this WM fibre tract was significantly associated with higher MDS. Since the anterior thalamic radiation contains fibres that connect the anterior nucleus of the thalamus with the anterior cingulate gyrus, which is part of the Papez circuit. Few studies have reported that a left thalamic lesion impairs memory for verbal materials[7] and a right thalamic lesion impairs memory for non-verbal materials[8]. These studies support our findings which showed correlation of elevated MD values in RATR fibre tract in hypothyroid patients.

Conclusion: Our results suggest that the microstructural changes in these WM fibre tracts may contribute to underlying dysfunction in memory in hypothyroidism. These findings provide further interesting insights into our understanding of the action of thyroid hormone in human brain.

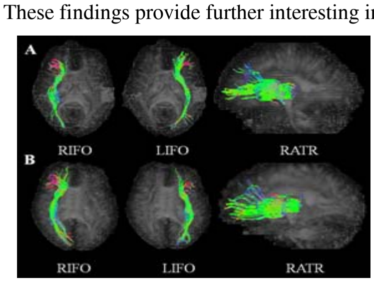

Fig.1: Projection of the RIFO and LIFO on mid-coronal plane and RATR on the mid-sagittal plane in age-matched control and hypothyroid patient. Patient (A) shows a decrease in fibre tracts compared with controls (B).

Table I shows Pearsons's correlation coefficient between memory dysfunction scores and DTI measures (FA and MD) of white matter fibres in controls and hypothyroid subjects.

Fibre Bundles	**Controls**		**Hypothyroids**	
	Memory dysfunction score vs FA			
	r value	p value	r value	p value
RIFO	0.104	0.807	-0.833	0.010*
LIFO	-0.384	0.347	-0.839	0.009*
	Memory dysfunction score vs MD			
RATR	0.268	0.520	0.836	0.010*

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